Mechanisms associated with age and sex modulate motor-like tics via the CB_2 cannabinoid receptor

Presented By:

Sharon Anavi-Goffer, Dr (Ph.D.)

Background

Δ^9-THC, the psychoactive compound in cannabis, is a partial-agonist of CB_1 and CB_2 receptors

- Can the CB_2 receptor modulate motor tics?
- Is this mechanism associated with sex?
- Is this mechanism associated with age?

Gorberg et al., Br J Pharmacol. 2020
Gorberg et al., Mol Neurobiol. 2022

Expression of functional CB_2 receptors on neurons in the brain

CB_2 receptor is expressed in the striatum and brainstem, where it regulates dopamine release:

- In adult male mice:
- JWH-133 (CB_2 receptor agonist) reduces adult locomotor activity.
- JWH-133 reduces cocaine-induced locomotor activity.
- HU-308 (5 mg/kg), CB_2 receptor agonist, reduces dyskinesia-like behavior in a model of Parkinson's.

There is a complex mechanism for the control of motor activity by the CB_2 receptor:

- HU-308 (40 mg/kg, i.p.) has no effect on the locomotor activity of adult female mice.

Gorberg et al., Mol Neurobiol. 2022

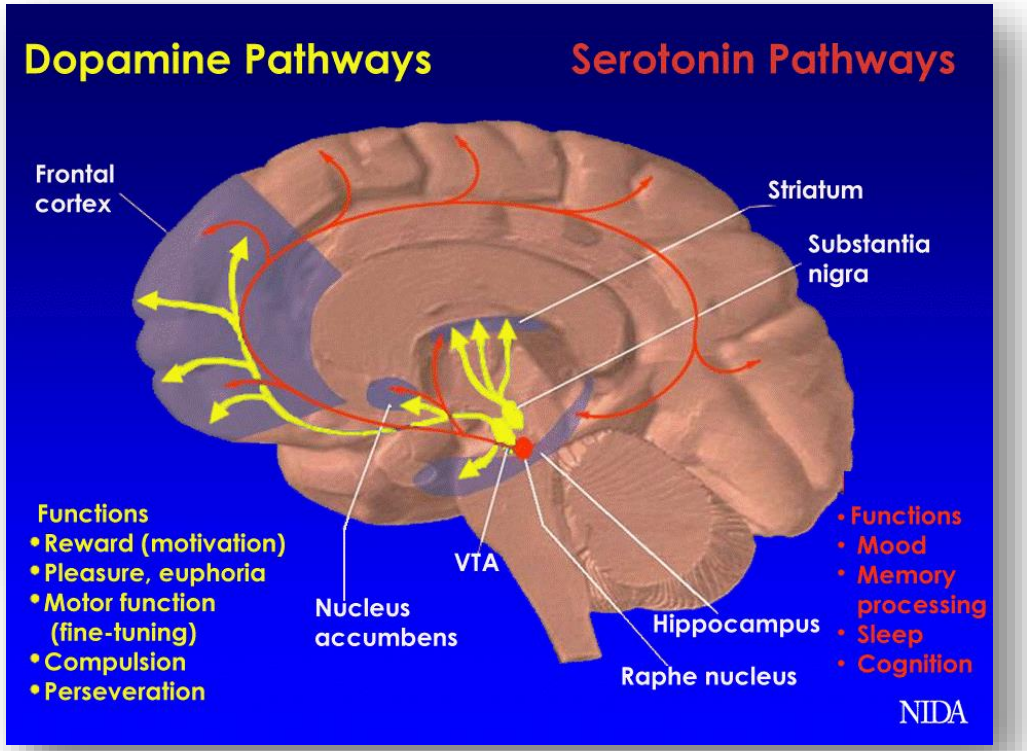
From patients to animal models

NIH Public Access
Author Manuscript
Neuropsychopharmacology. Author manuscript; available in PMC 2013 June 30.

Published in final edited form as:
Neuropsychopharmacology. 2008 May ; 33(6): 1239–1251. doi:10.1038/sj.npp.1301528.

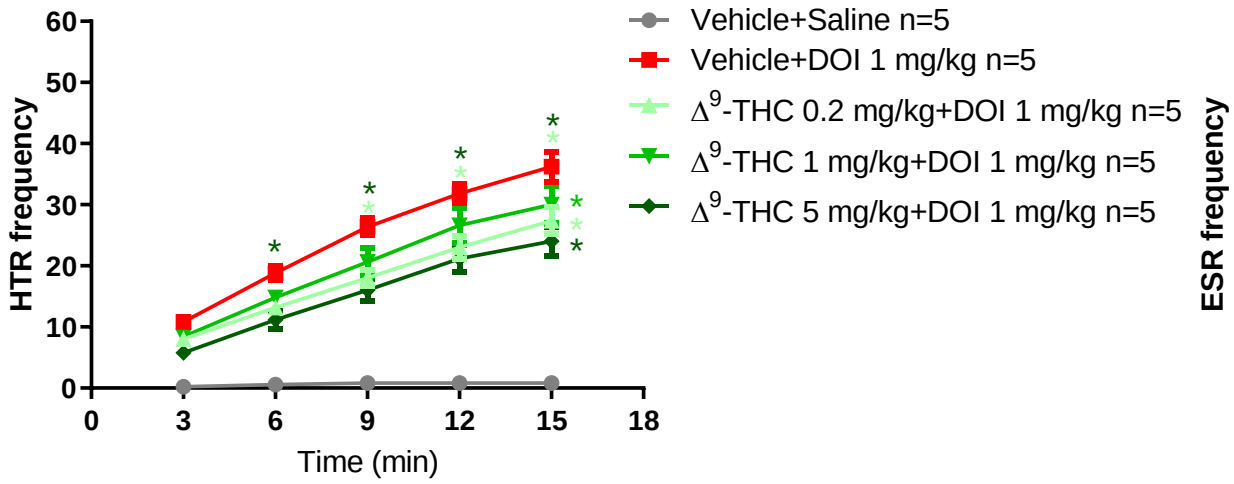
Mechanisms of Dopaminergic and Serotonergic Neurotransmission in Tourette Syndrome: Clues from an in vivo Neurochemistry Study with PET

Dean F. Wong[1,2], James R. Brašić[1], Harvey S. Singer[3], David J. Schretlen[2], Hiroto Kuwabara[1], Yun Zhou[1], Ayon Nandi[1], Marika A. Maris[1], Mohab Alexander[1], Weiguo Ye[1], Olivier Rousset[1], Anil Kumar[1], Zsolt Szabo[1], Albert Gjedde[5], and Anthony A. Grace[4]

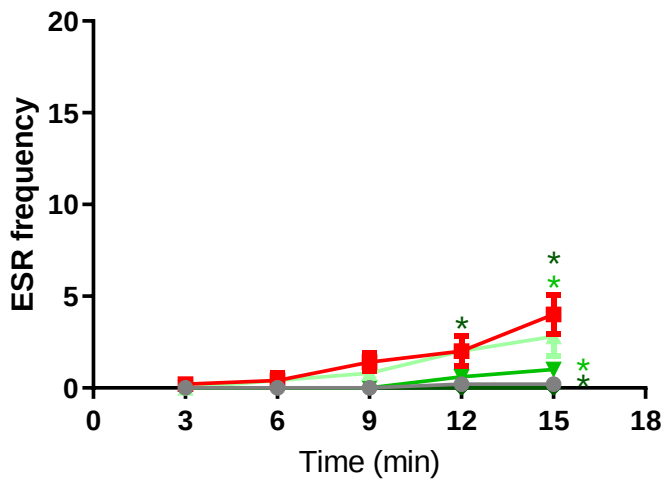


Effects of Δ^9-THC on DOI-induced tic-like behaviour of juvenile males

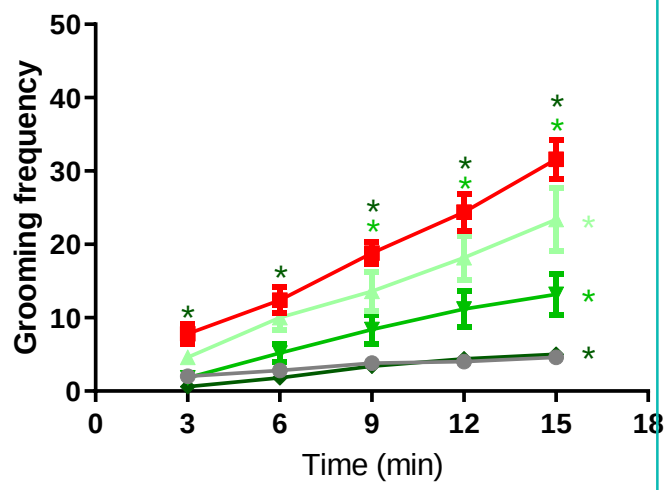
Central motor-like tic
HTR



Urge-like response
ESR



Caudally located motor-like tic
Grooming



Gorberg et al., Br J Pharmacol. 2020

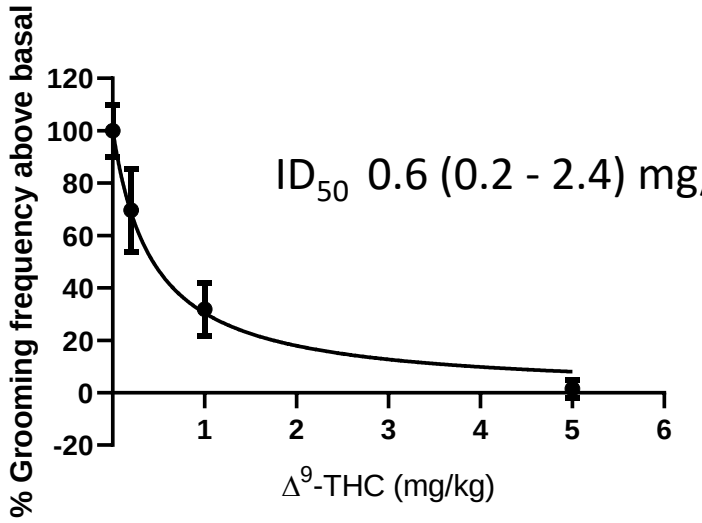
- **~ 34% reduction of HTR**
- **Catalepsy at 5 mg/kg Δ^9-THC**

Δ^9-THC: Decision making (Gorberg et al., Br J Pharmacol. 2020)

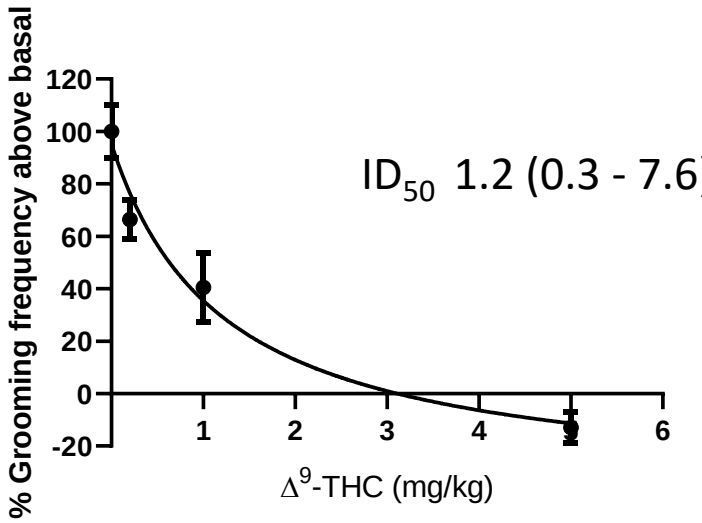
Juvenile mice

Young adult mice

Caudally located motor-like tic

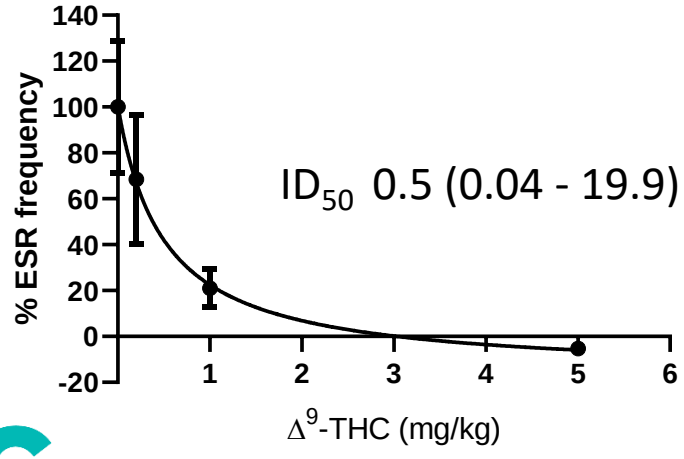


ID_{50} 0.6 (0.2 - 2.4) mg/kg

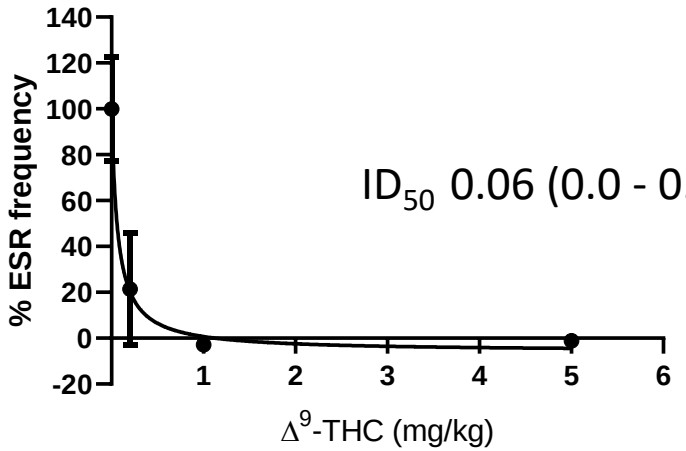


ID_{50} 1.2 (0.3 - 7.6) mg/kg

Urge-like response



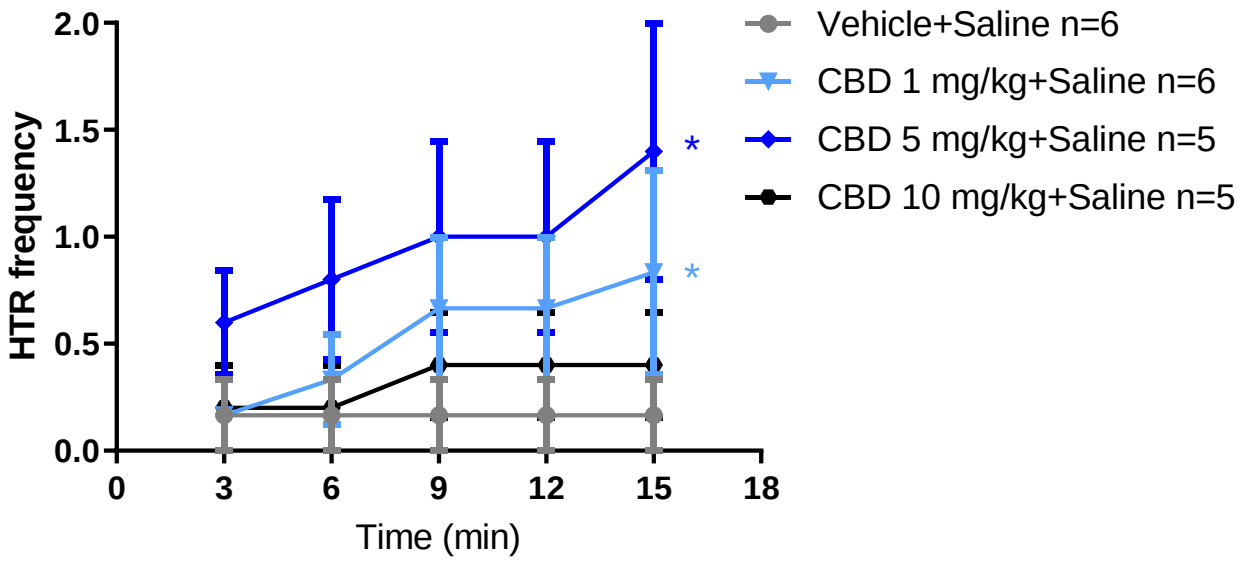
ID_{50} 0.5 (0.04 - 19.9) mg/kg



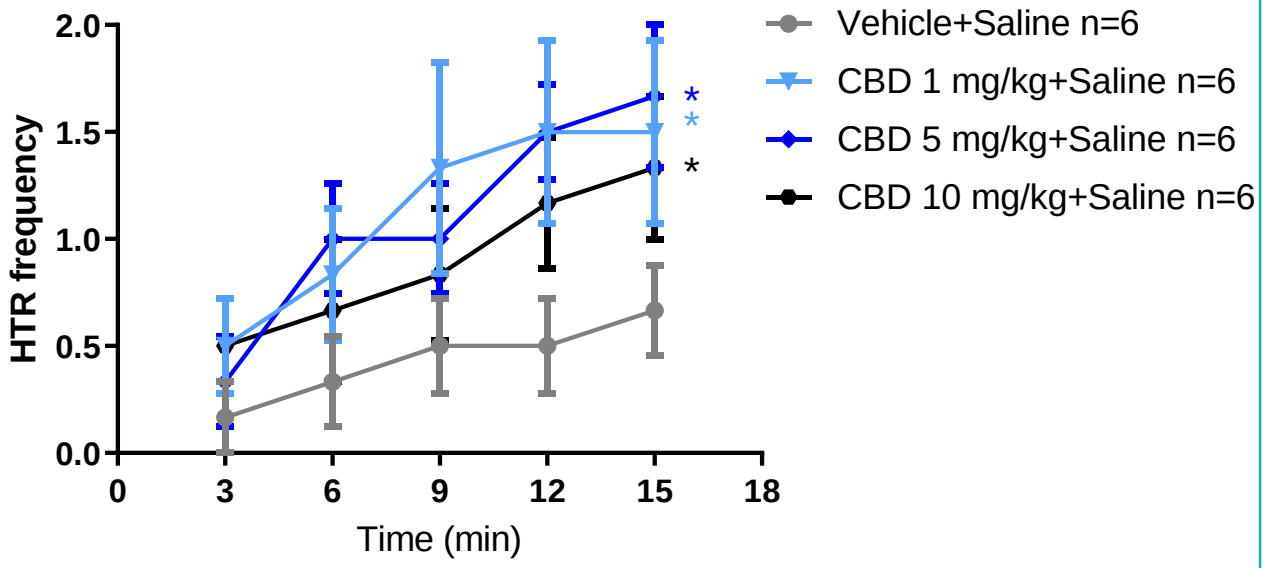
ID_{50} 0.06 (0.0 - 0.4) mg/kg

CBD increases motor-like tics

Juvenile mice



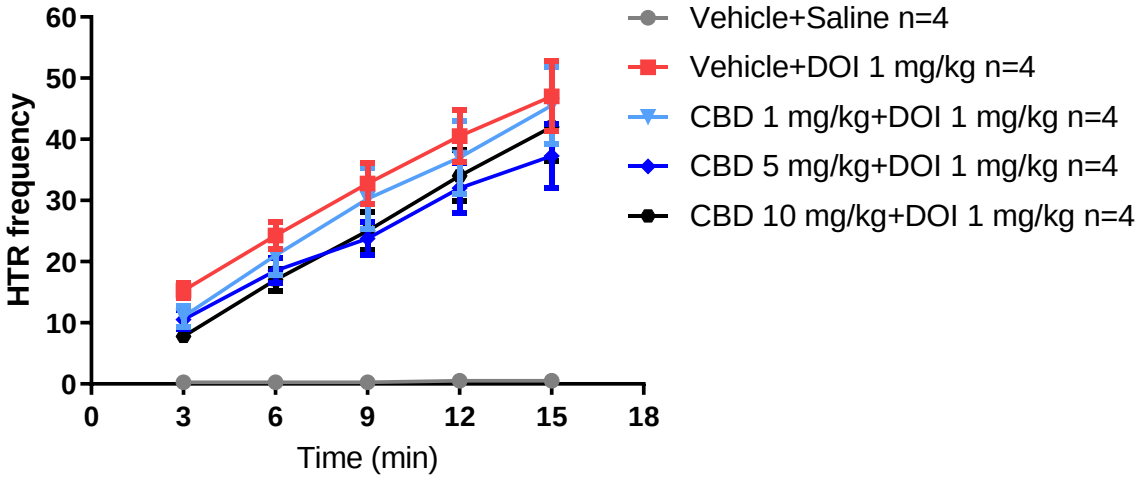
Young adult mice



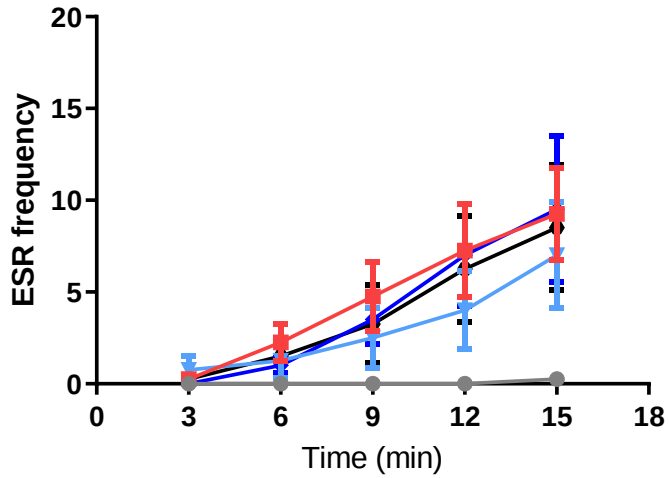
Gorberg et al., Br J Pharmacol. 2020

CBD has no effect on DOI-induced motor-like tics in juvenile male mice

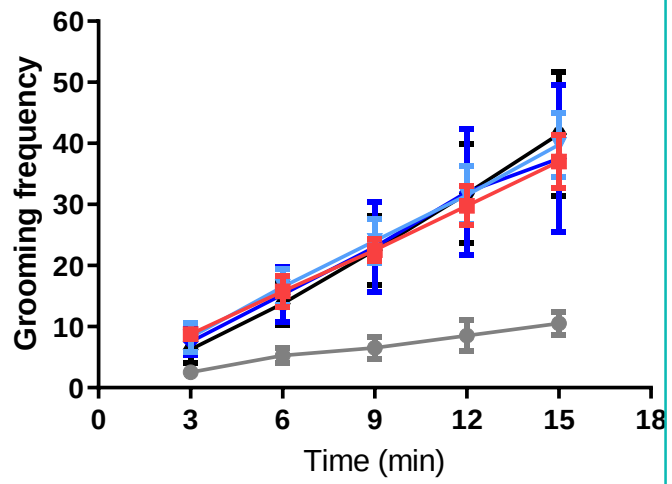
Central motor-like tic
HTR



Urge-like response
ESR



Peripheral motor-like tic
Grooming



Gorberg et al., Br J Pharmacol. 2020

Results with Δ^9-THC and CBD are published

Gorberg V, **McCaffery** P, **Anavi-Goffer** S.

Different responses of repetitive behaviours in juvenile and young adult mice to Δ^9-tetrahydrocannabinol and cannabidiol may affect decision making for Tourette syndrome.

Br J Pharmacol. 2020

This study was supported by a Research Grant Award from the **Tourette Association of America**

Objectives

Can the CB_2 receptor modulate motor tics?

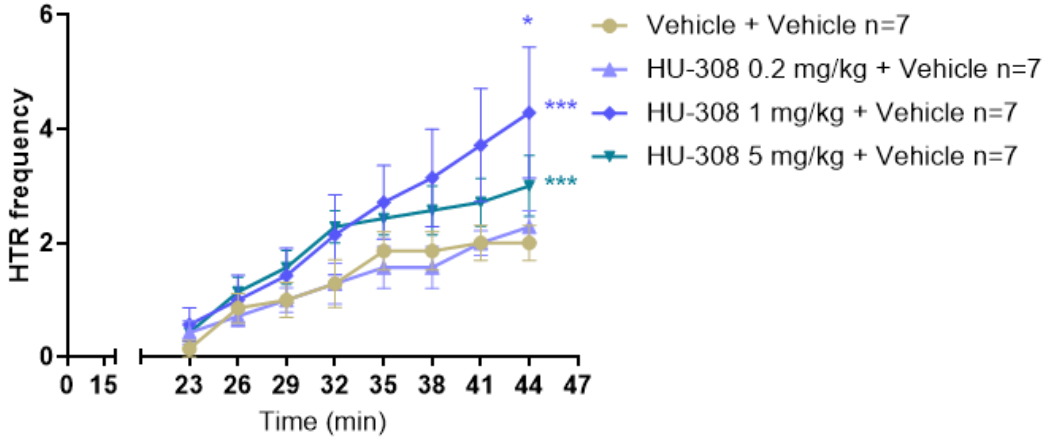
1. What are the effects of **HU-308**, a selective CB_2 receptor agonist, on motor-like tics?
2. What are the effects on motor-like tics of HU-308 in the presence of **DOI**, a highly potent agonist of the serotonin $5\text{-}HT_{2A/2C}$ receptors?
3. What are the effects of HU-308 on motor-like tics of CB_2 receptor knockout ($\mathbf{CB_2^{-/-}}$) mice?

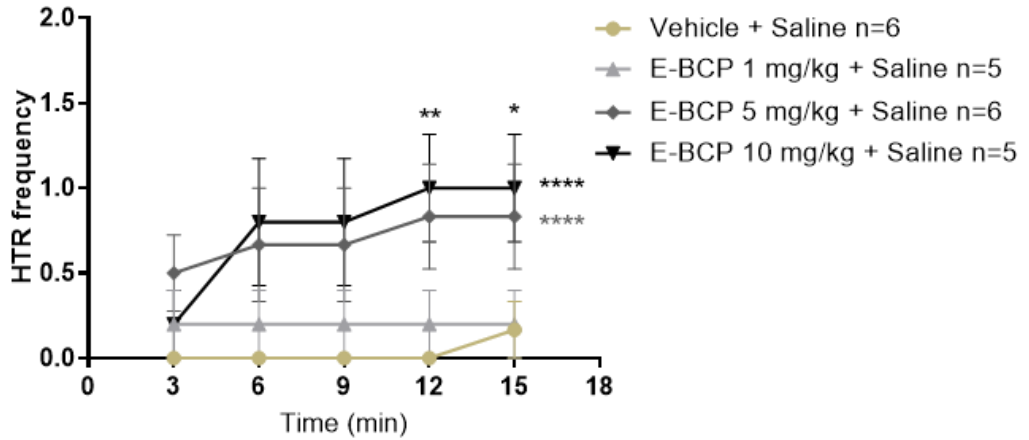
Gorberg et al., Mol Neurobiol. 2022

CB_2 receptor agonists increase motor-like tics in juvenile males

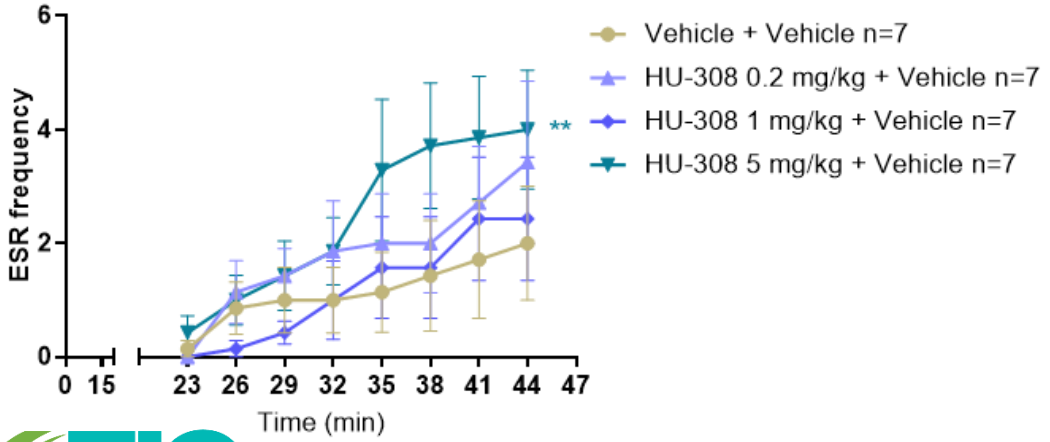
Gorberg et al., Mol Neurobiol. 2022

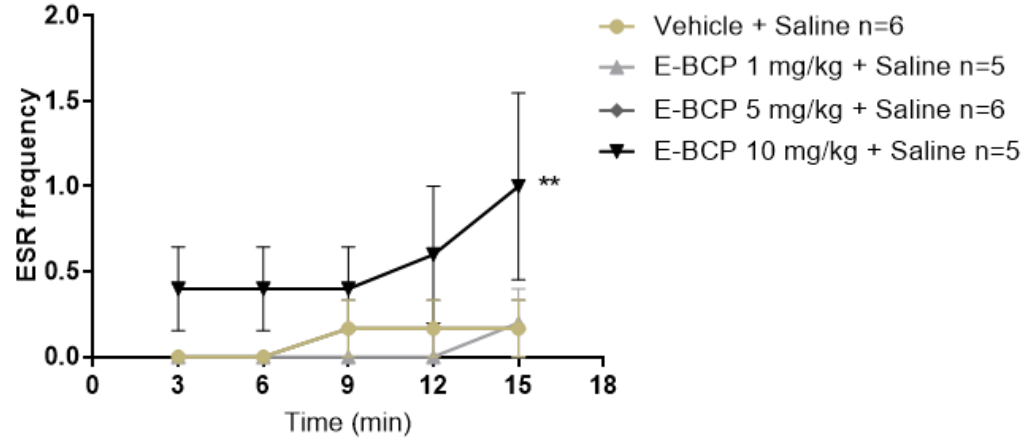
HTR





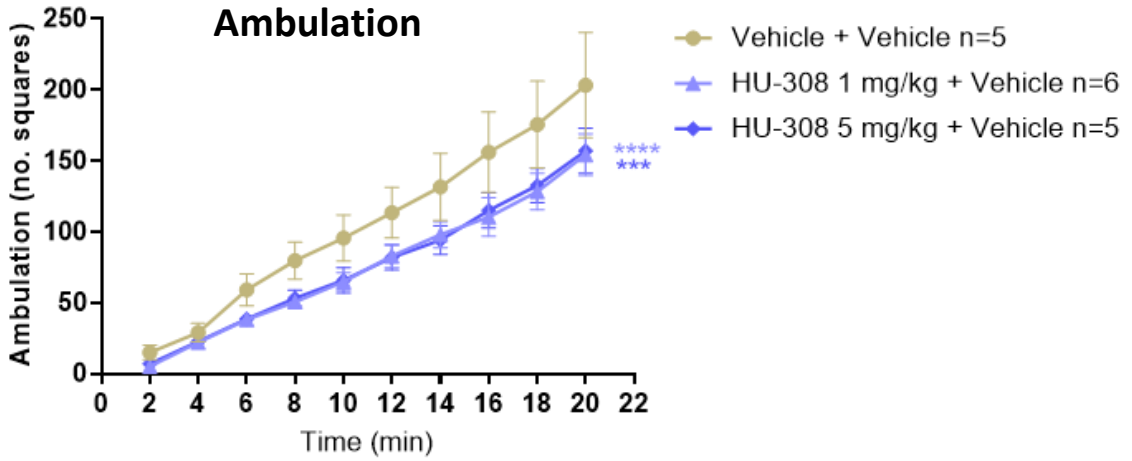
ESR

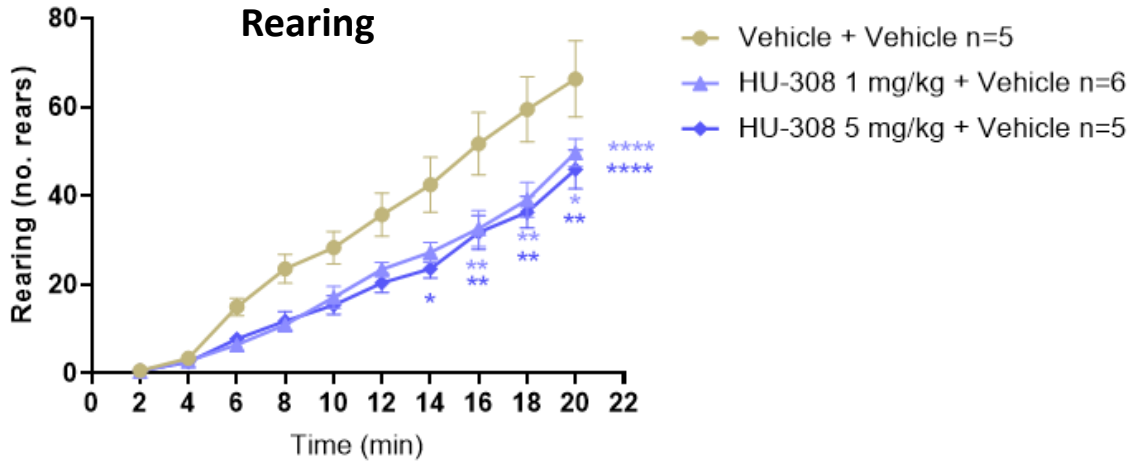


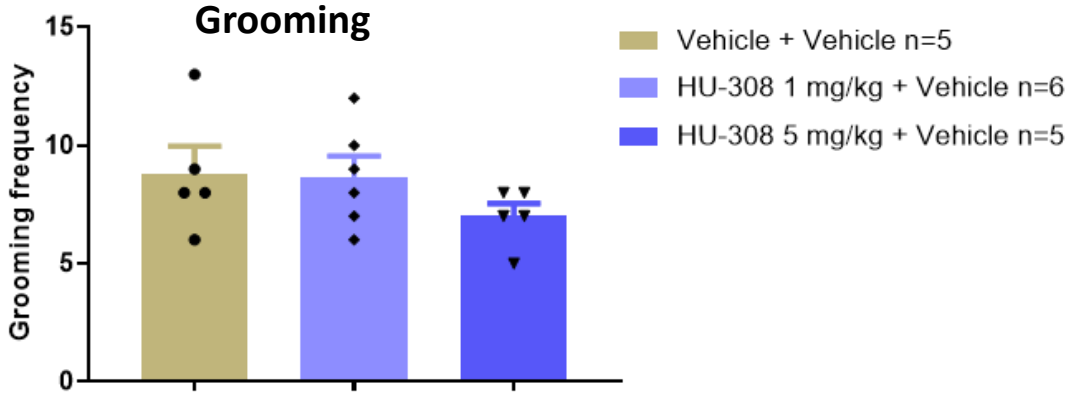


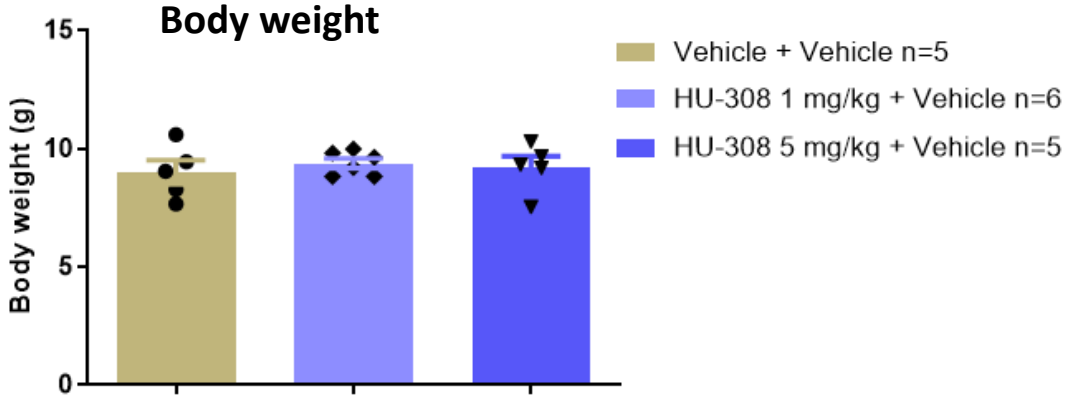
HU-308, a CB_2 receptor agonist, reduces locomotor activity in juvenile males

Gorberg et al., Mol Neurobiol. 2022









Conclusion & Implication

The increased HTR and ESR in juvenile mice

that was induced by

CB_2 receptor agonists suggests that

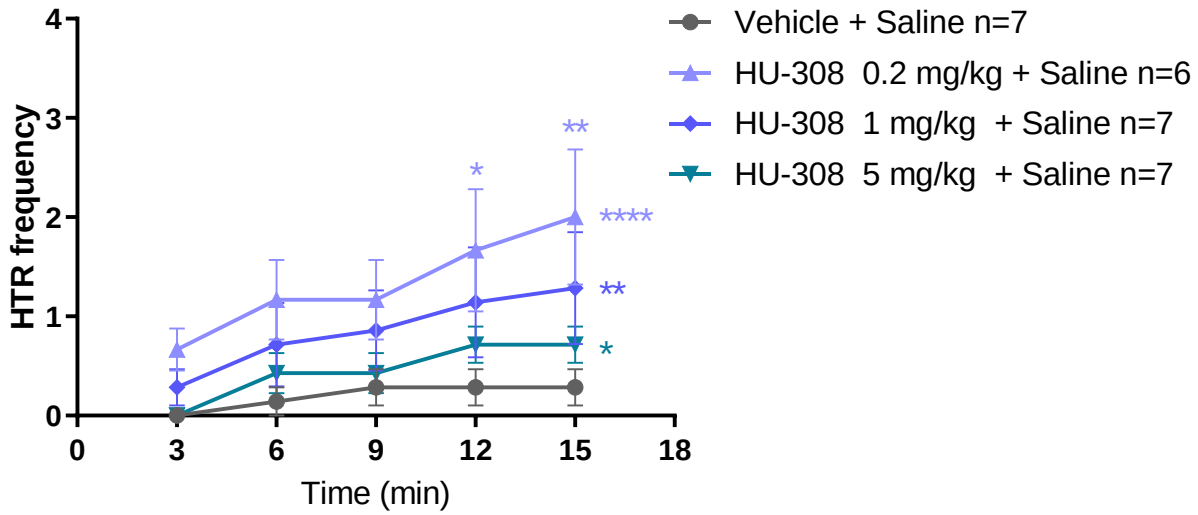
stimulation of the CB_2 receptor

may generate motor tics in children

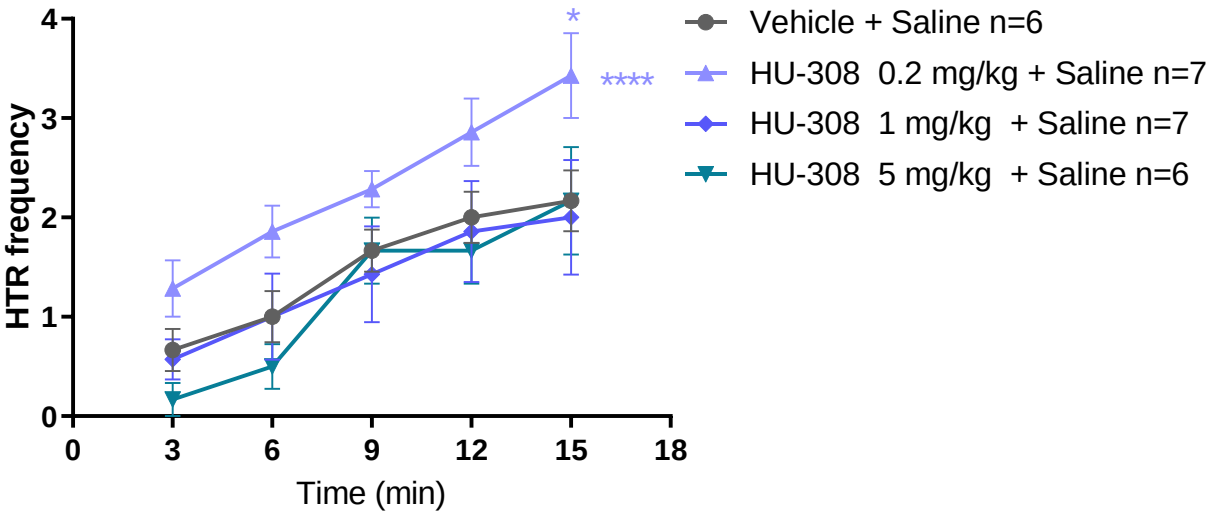
Gorberg et al., Mol Neurobiol. 2022

HU-308 has a lower or no effect on HTR in juvenile females

Juvenile males



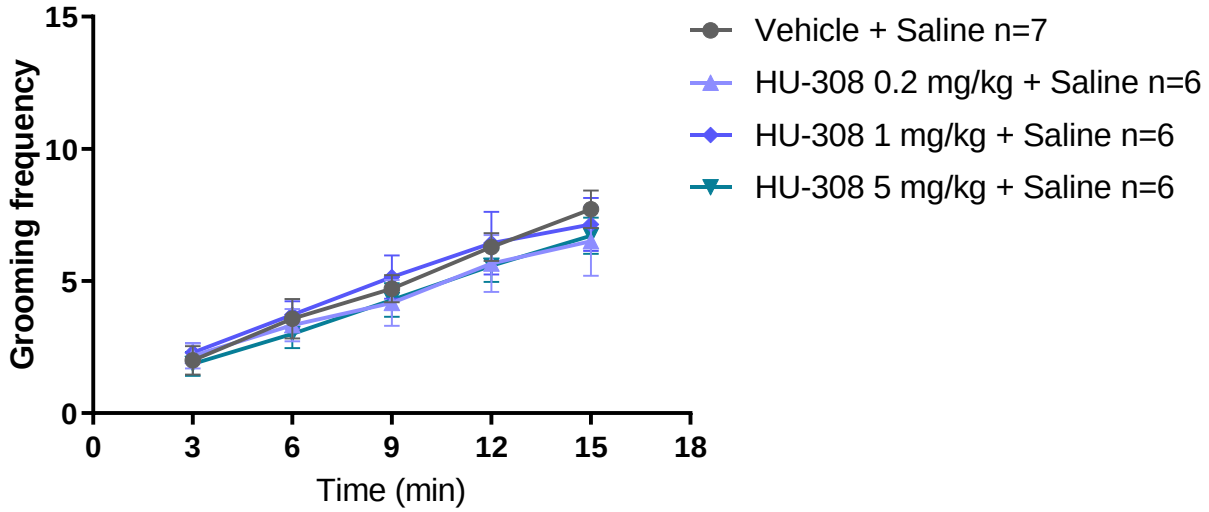
Juvenile females



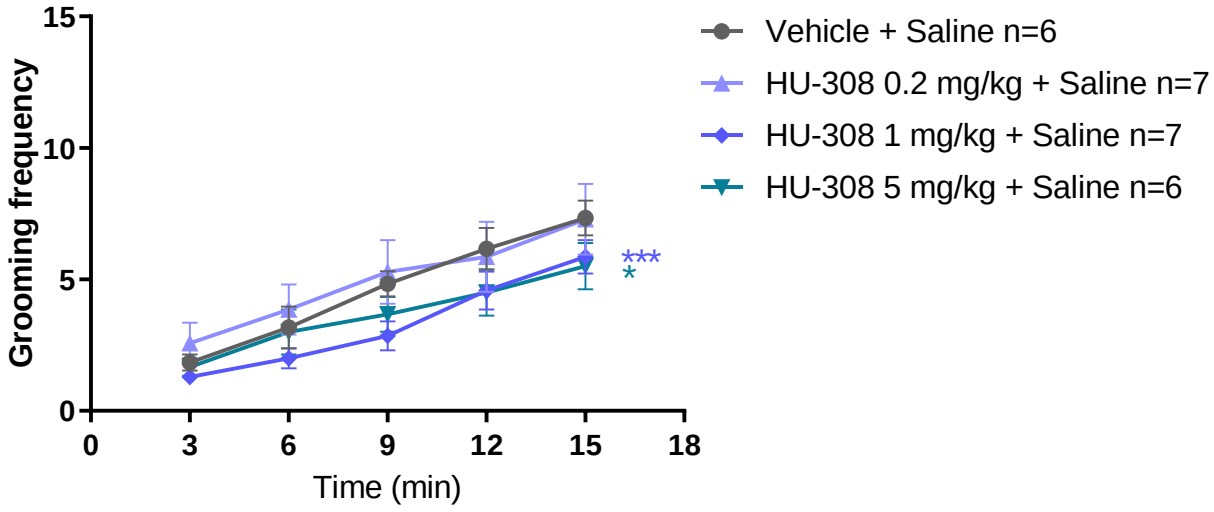
Gorberg et al., Mol Neurobiol. 2022

HU-308 significantly decreases basal grooming behavior in juvenile females but not in males

Juvenile males



Juvenile females



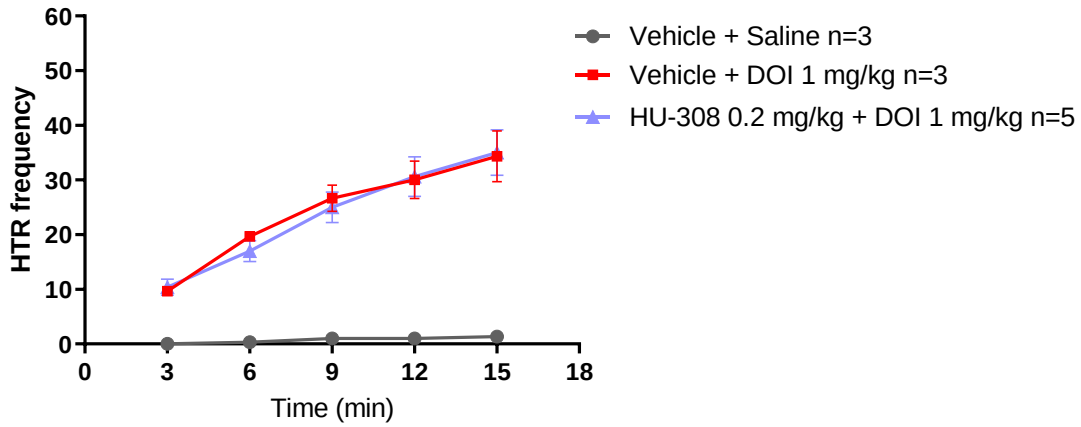
Gorberg et al., Mol Neurobiol. 2022

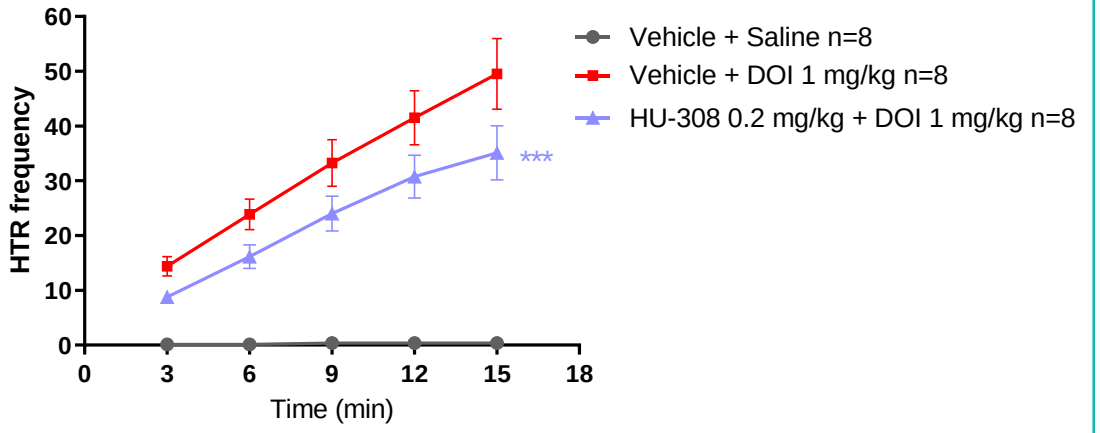
HU-308 (0.2 mg/kg) significantly inhibits DOI-induced motor-like tics in females but not in males

Juvenile males

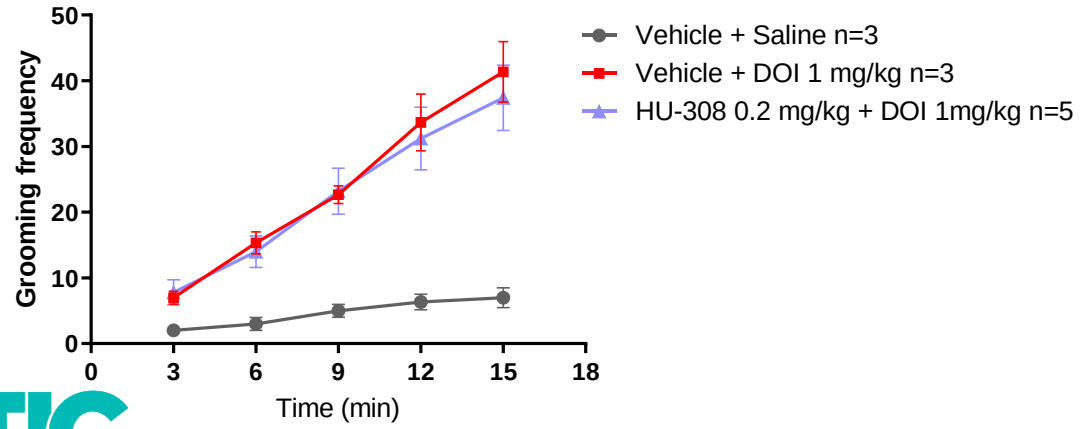
Juvenile females

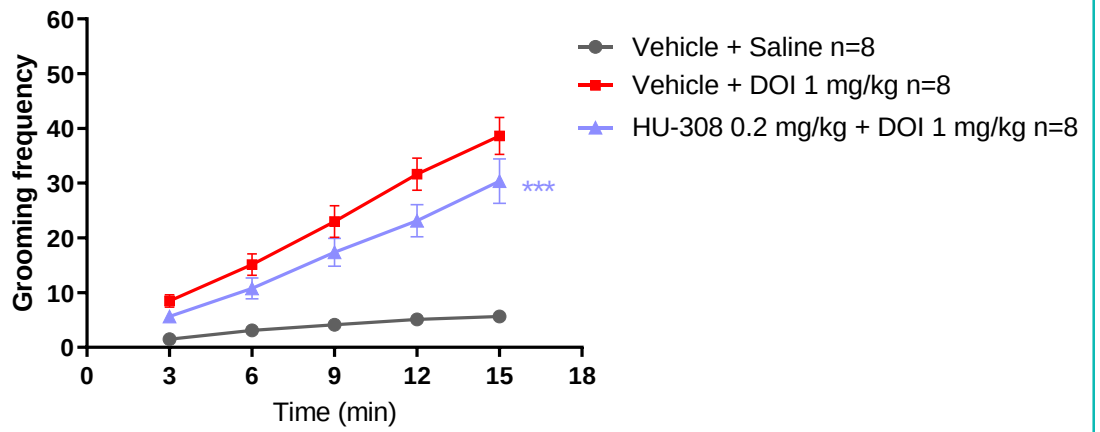
HTR





Grooming





Gorberg et al., Mol Neurobiol. 2022

Conclusion & Implication

- HU-308 (0.2 mg/kg) significantly inhibits DOI-induced HTR and grooming behavior in females but not in males.
- The CB_2 receptor stimulation may possibly reduce the frequency of caudally located motor tics in girls.
- **The CB_2 receptor contributes to the skewed ratio between boys and girls with Tourette syndrome, increasing the prevalence of Tourette syndrome in boys.**

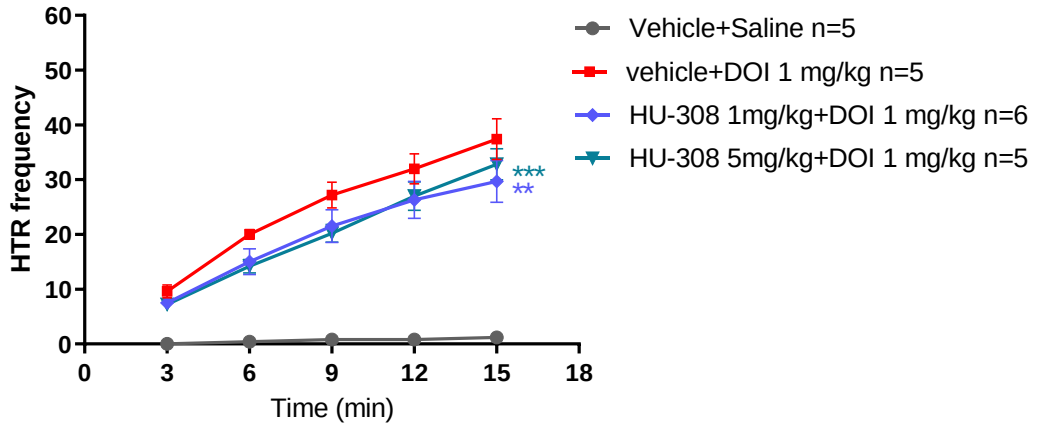
Gorberg et al., Mol Neurobiol. 2022

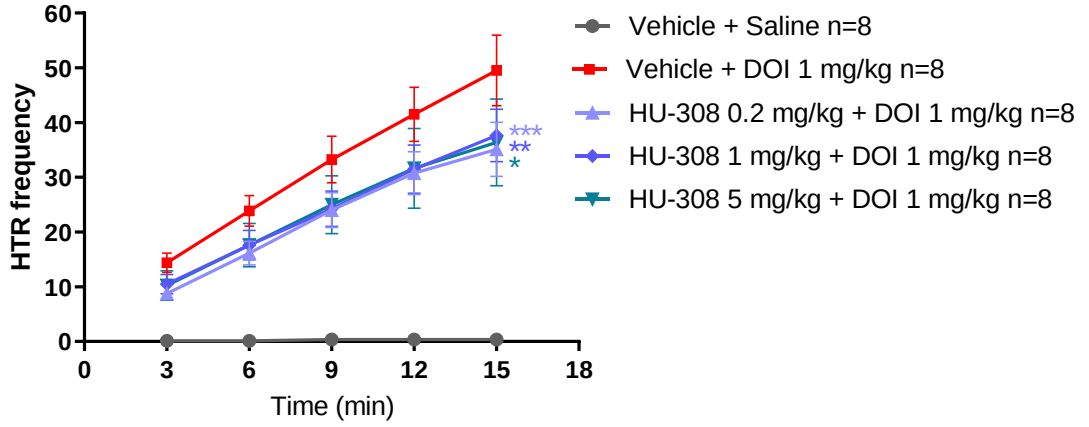
HU-308 (1, 5 mg/kg) reduces DOI-induced motor-like tics

Juvenile males

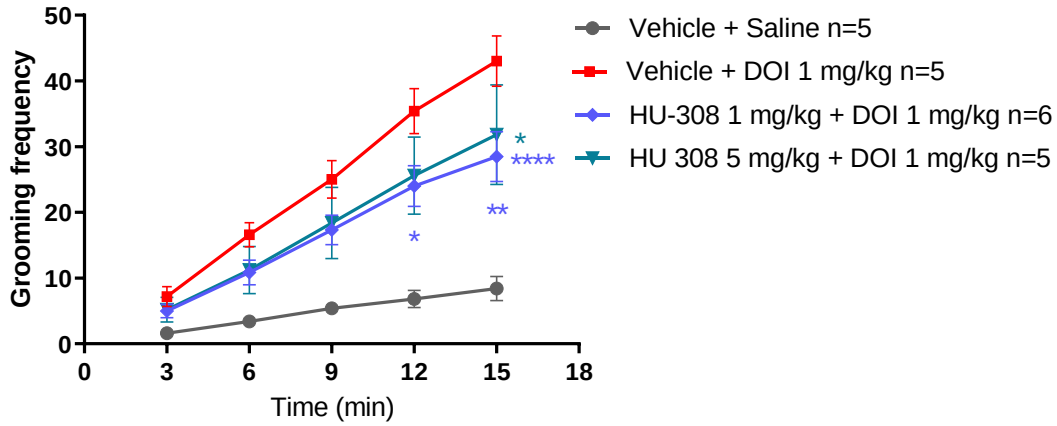
Juvenile females

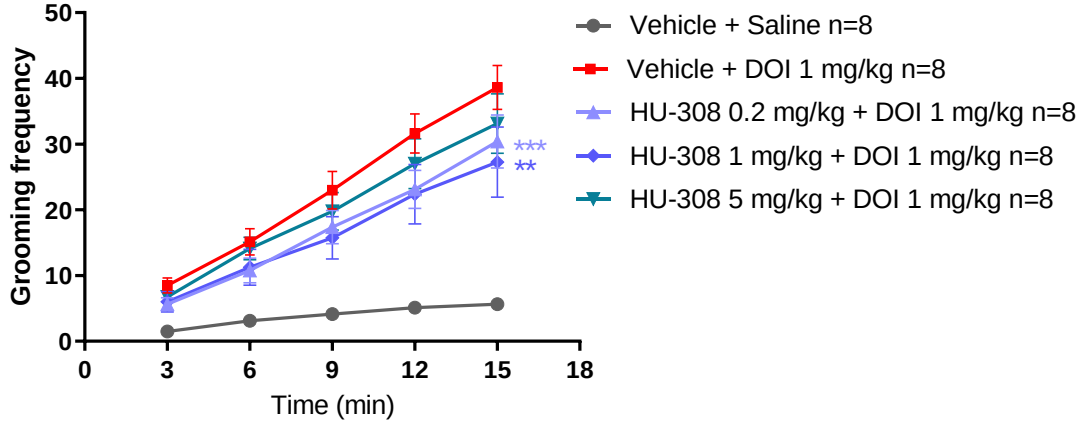
HTR





Grooming





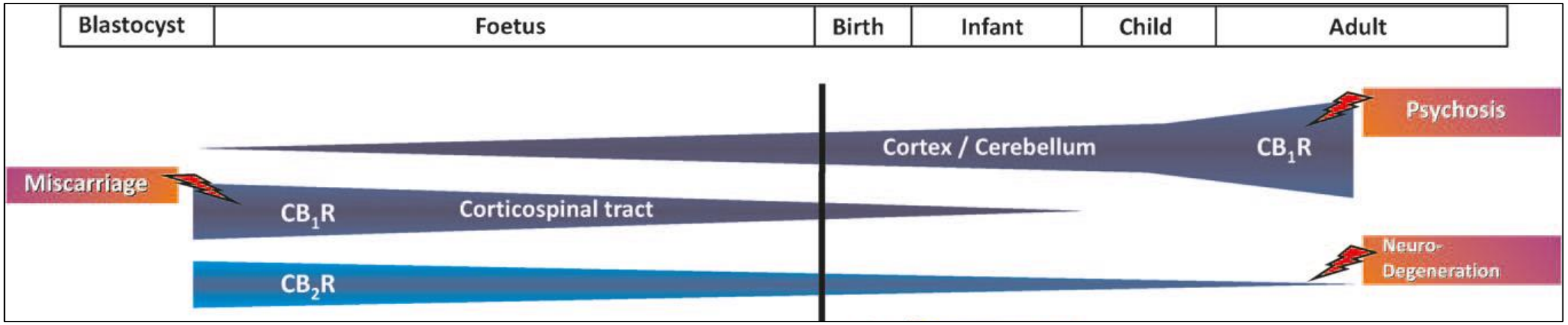
Gorberg et al., Mol Neurobiol. 2022

Conclusions & Implications

- CB_2 receptors modulate 5-$HT_{2A/2C}$-induced motor tics in males and females
- The CB_2 receptor contributes to the skewed ratio between boys and girls with Tourette syndrome

Gorberg et al., Mol Neurobiol. 2022

Is this mechanism associated with age?



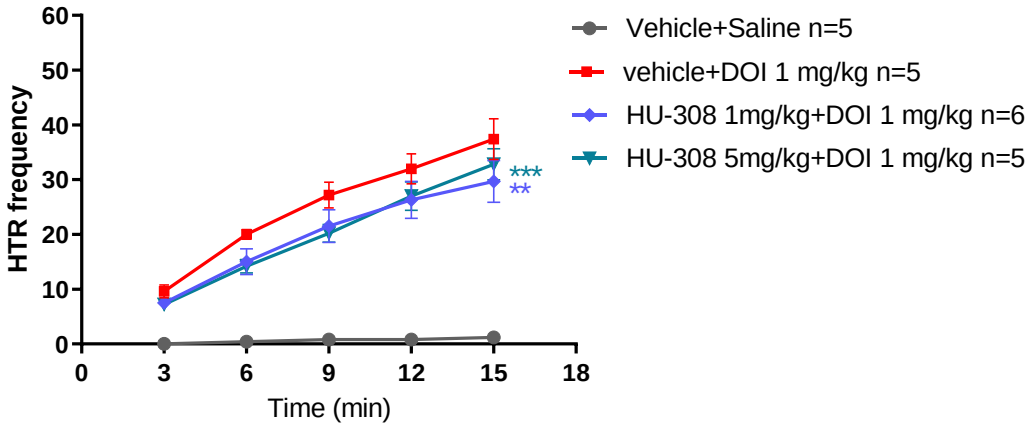
Anavi-Goffer & Mulder. ChemBioChem 2009

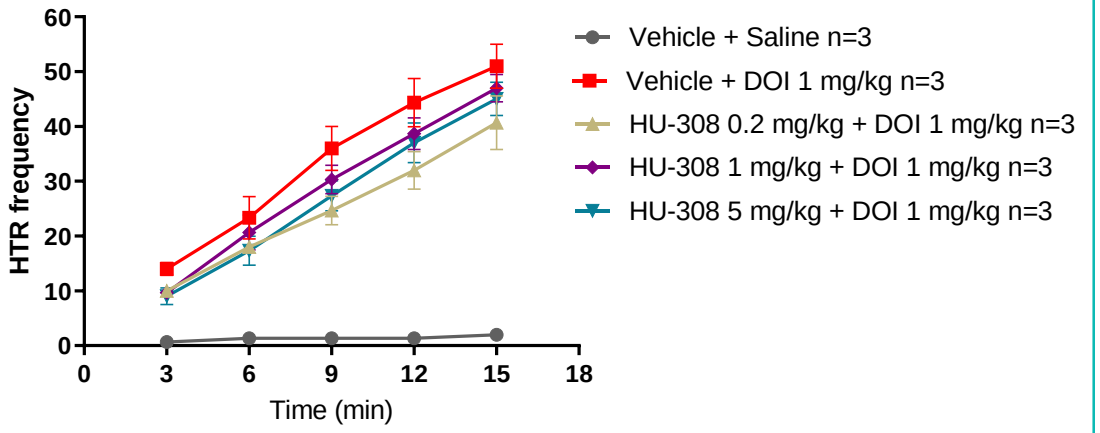
Age difference in the effect of HU-308 DOI-induced motor-like tics

Juvenile males

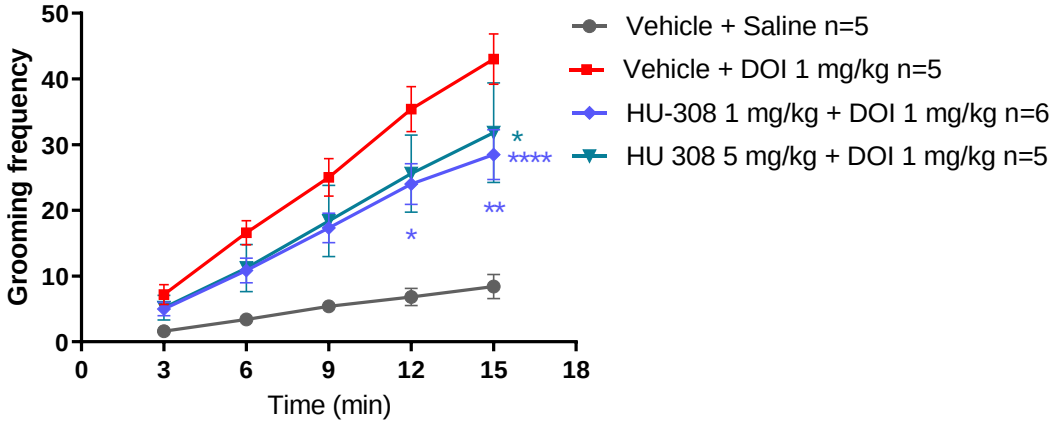
Young adult males

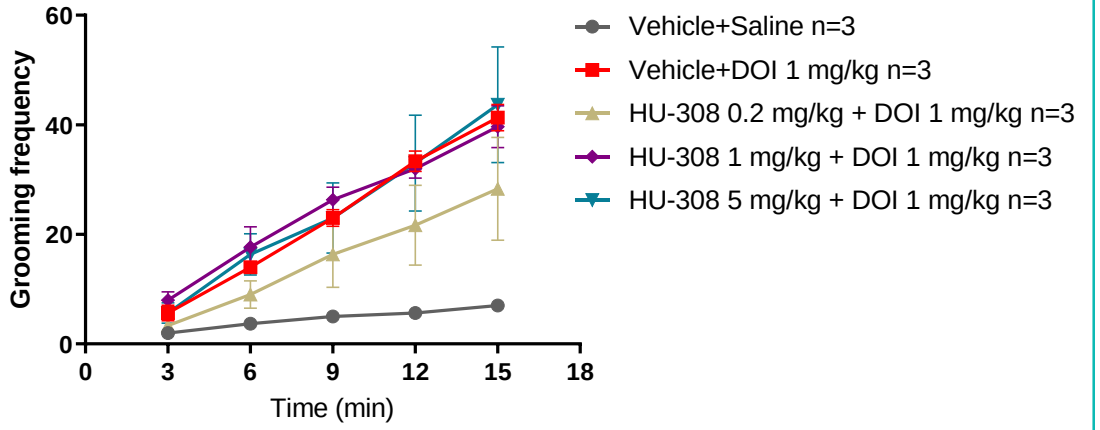
HTR





Grooming





Conclusion

The CB_2 receptor mechanism that modulates

$5\text{-}HT_{2A/2C}$-induced motor-like tics is

associated with age

Gorberg et al., Mol Neurobiol. 2022

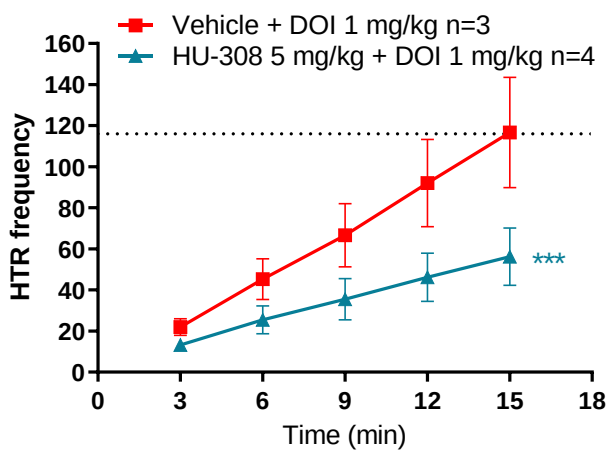
Physiol Rev 99: 1877–2013, 2019

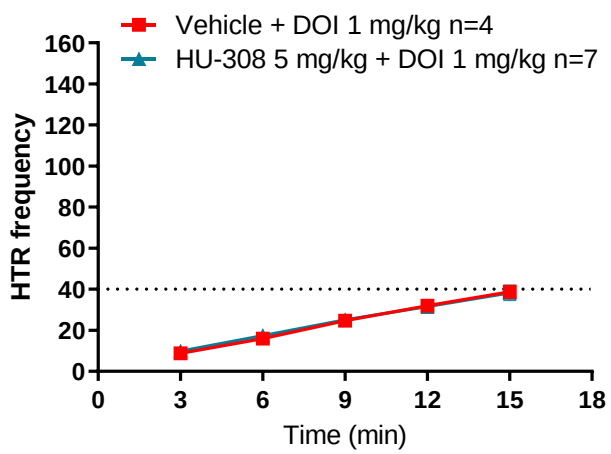
The effects of HU-308 in adult male mice

Adult males CB2$^{-/-}$ mice

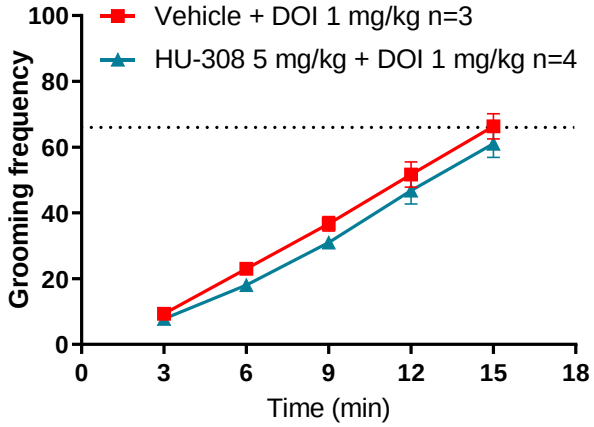
Adult males C57BL/6J mice

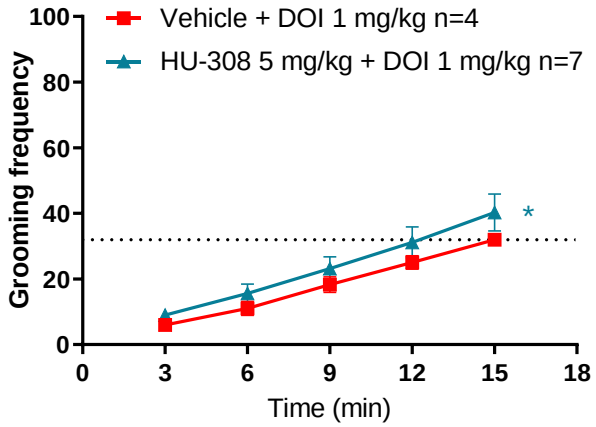
HTR





Grooming



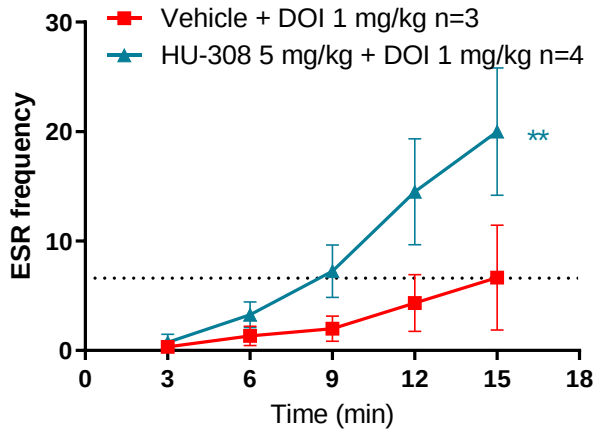


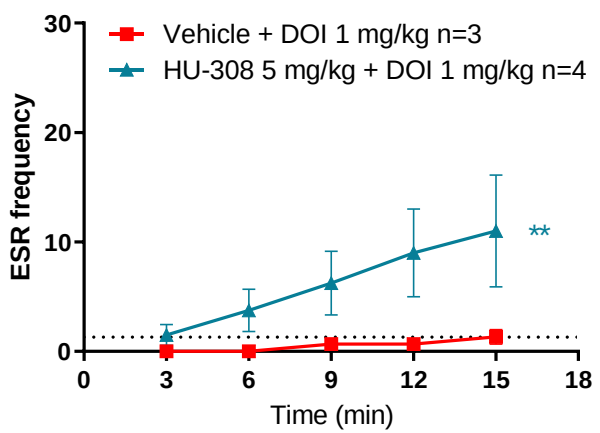
Gorberg et al., Mol Neurobiol. 2022

The effects of HU-308 in adult female mice

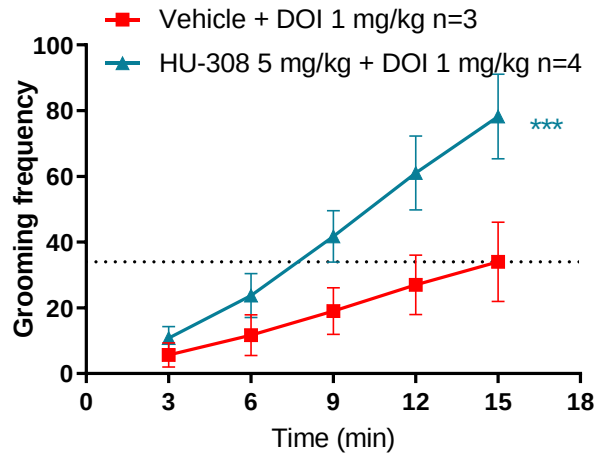
Adult females CB2$^{-/-}$ mice | **Adult females C57BL/6J mice**

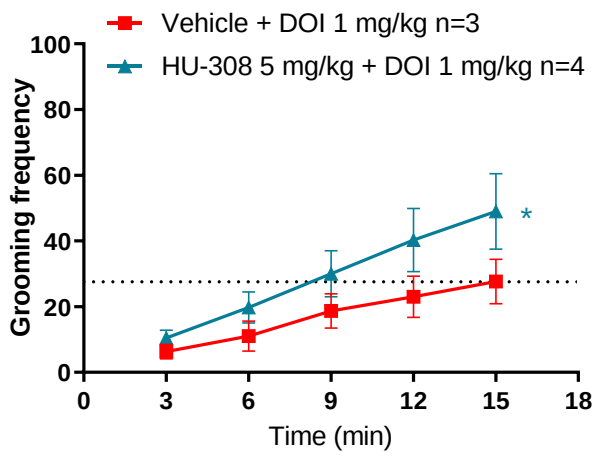
ESR





Grooming





Gorberg et al., Mol Neurobiol. 2022

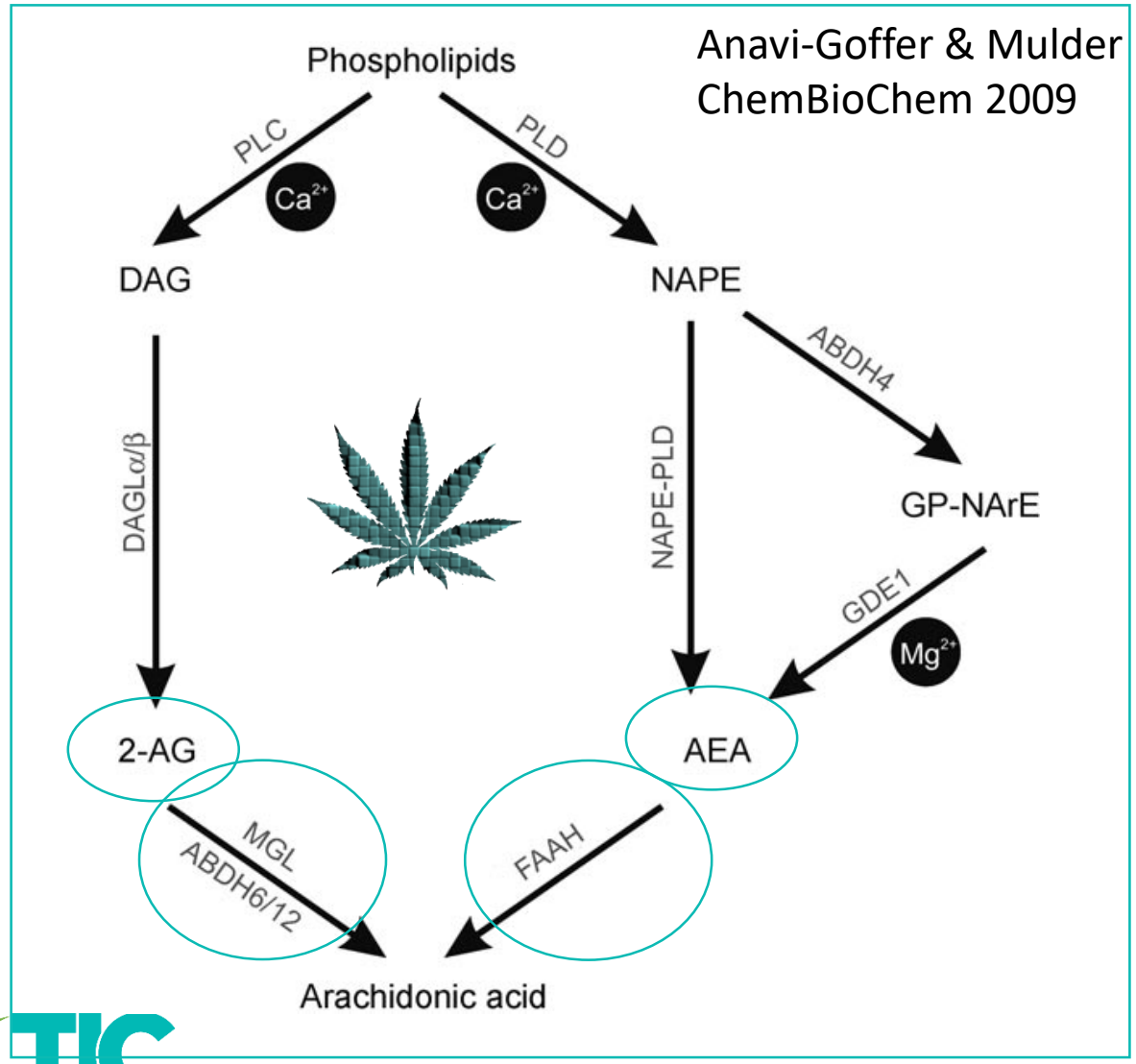
Conclusion & Implications

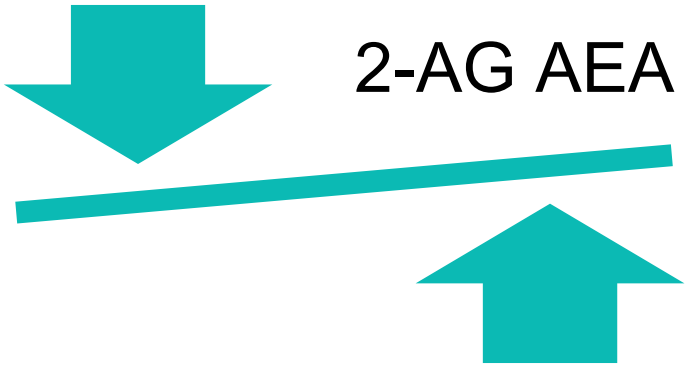
HU-308 has an off-target effect which increases 5-$HT_{2A/2C}$-induced motor-like tics in adult female mice

Discovering a new target that modulate motor tics will promote the development of new drugs

Gorberg et al., Mol Neurobiol. 2022

Endocannabinoid synthesising and degrading pathways





A reduction in catabolic enzyme expression level will increase 2-AG and AEA levels

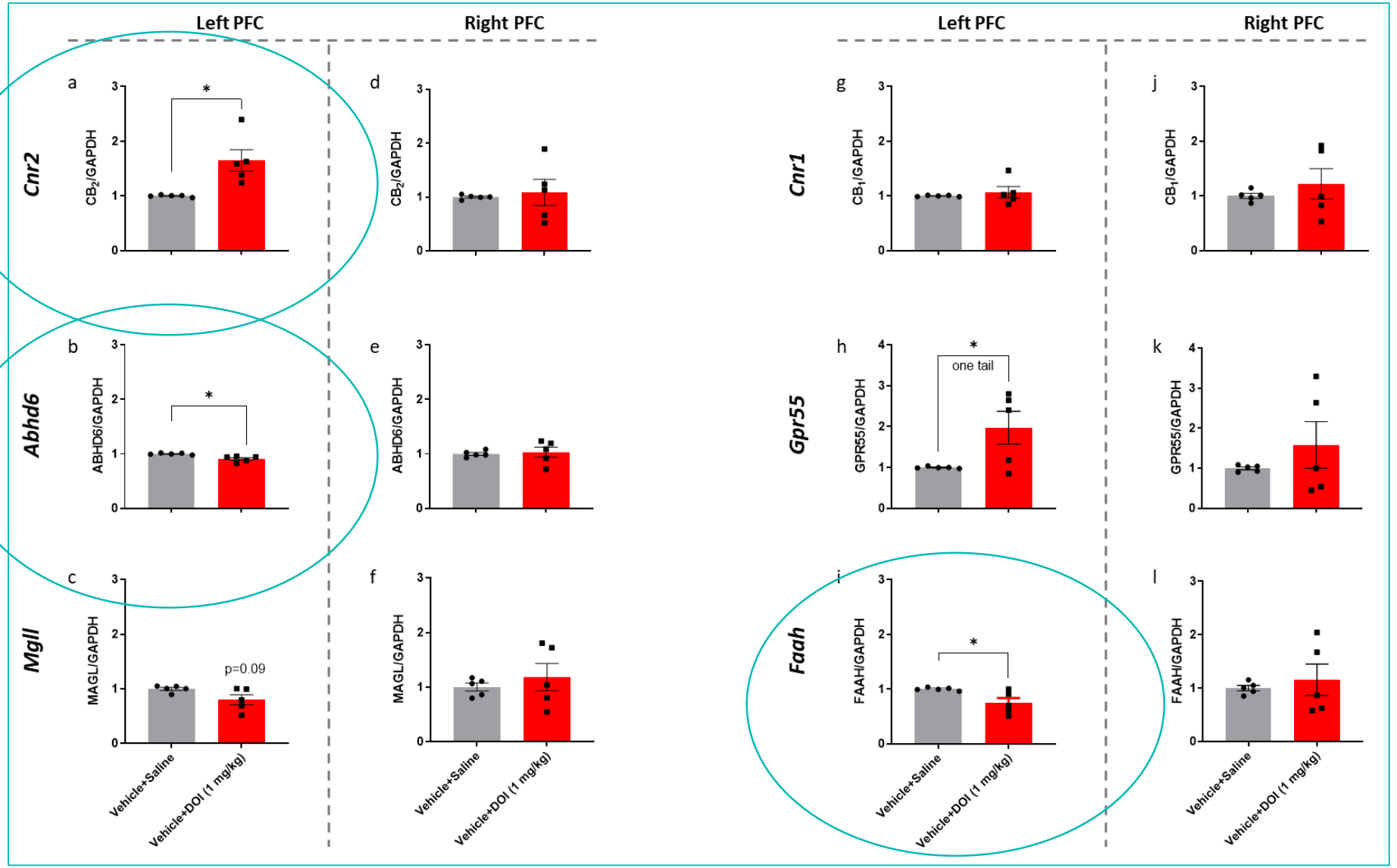
PCR results DOI-induced motor tics

In left prefrontal cortex of juvenile male mice

CB_2 receptor

α/β-Hydrolase domain-containing 6 (ABHD6)

Fatty acid amide hydrolase (FAAH)



Implications

Acute

2-AG from M4 muscarinic receptors on striatal D1-medium spiny neurons (MSNs) stimulate CB_2 receptors on dopaminergic terminals

Sustained

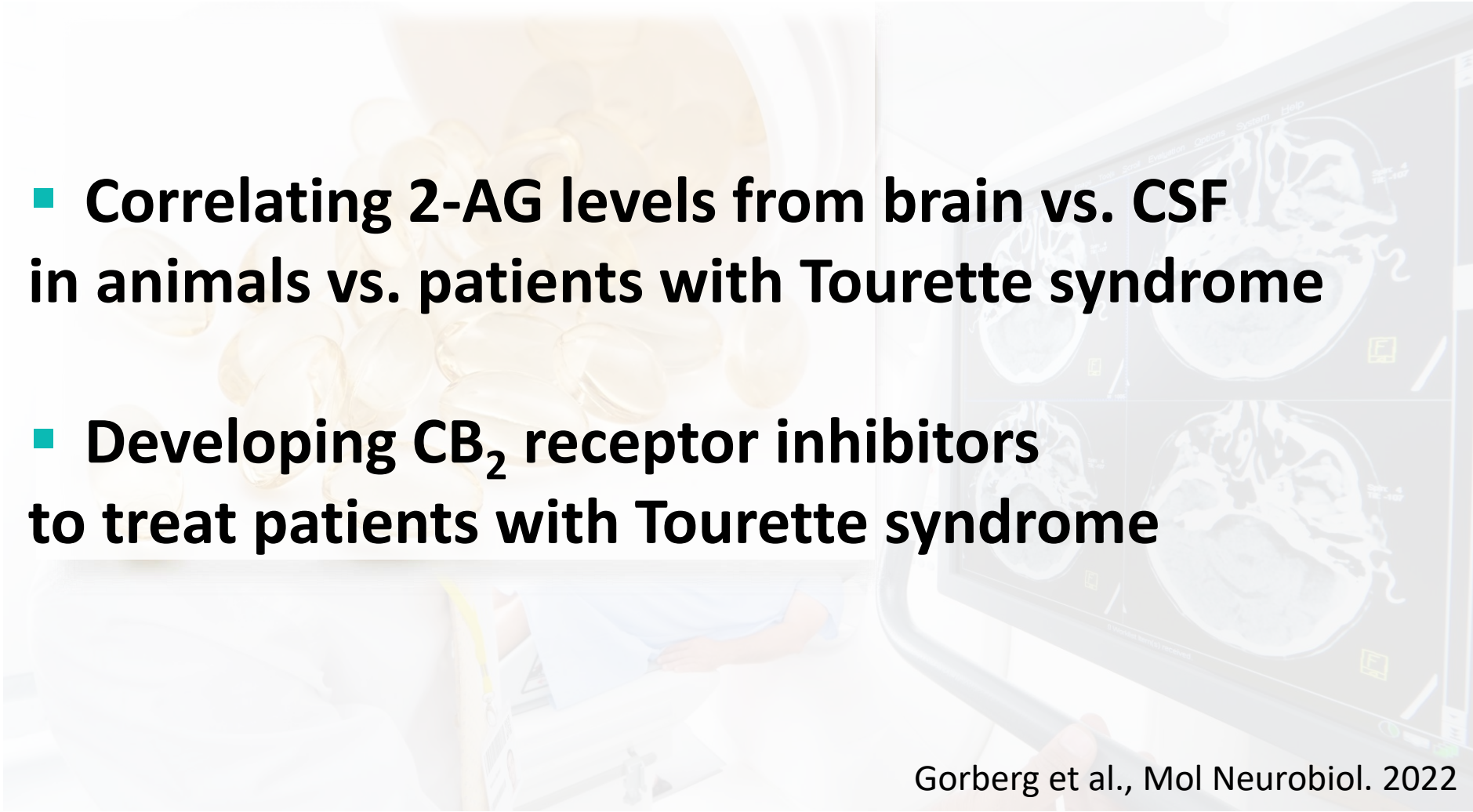
A clinical study found increased 2-AG & AEA levels in the CSF of patients with TS

Gorberg et al., Mol Neurobiol. 2022

Implications

- **Correlating 2-AG levels from brain vs. CSF in animals vs. patients with Tourette syndrome**

- **Developing CB_2 receptor inhibitors to treat patients with Tourette syndrome**



Gorberg et al., Mol Neurobiol. 2022

THANK YOU

Gorberg V, **Borisov** V, **Greig** IR, **Pertwee** RG, **McCaffery** P, **Anavi-Goffer** S.

Motor-like Tics are Mediated by CB_2 Cannabinoid Receptor-dependent and Independent Mechanisms Associated with Age and Sex.

Mol Neurobiol. 2022.

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